Uncoupled neuro-osseous growth in adolescent idiopathic scoliosis? A preliminary study of 90 adolescents with whole-spine three-dimensional magnetic resonance imaging

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Abstract Previous literatures revealed abnormal cross-sectional morphology of spinal cord in AIS, suggesting the presence of disproportional growth between the neural and skeletal system. No accurate measurement of whole spine by MRI multiplanar reconstruction and their correlation with Cobb angle were studied. In this study, MRI three-dimensional reconstruction of the whole spine was performed in 90 adolescents (49 AIS with thoracic/thoracolumbar curve, and 41 age-matched healthy controls). Measurements of the ratio of anteroposterior (AP) and transverse (TS) diameter of the cord, the concave and convex lateral cord space (LCS) were obtained at the apical level in AIS patients. Cerebellar tonsillar level related to the basion-opisthion line, location of conus medullaris, cord length, vertebral column length, cord/vertebral column length ratio were obtained. All of the same parameters were also measured in healthy controls at matched vertebral levels and their correlations with Cobb angle were made. We notice that AP, TS, AP/TS and LCS ratio were increased in AIS subjects with low-lying position of cerebellar tonsillar level and elevating position of conus medullary when compared with healthy controls ($P < 0.01$). AP, AP/TS and LCS ratio were correlated significantly with Cobb angle ($P < 0.05$). Cord length and vertebral column

length were not significantly different between AIS and control group. However, cord/vertebral column length ratio was significantly smaller in AIS group ($P < 0.01$). Cord length, vertebral column length and cord/vertebral column length ratio were not related with age or Cobb angle ($P > 0.05$). These data suggest the presence of uncoupled neuro-osseous growth along the longitudinal axis of spinal cord with associated morphologic changes of cross-sectional configuration and relative position of the cord. Some changes are significantly relevant with Cobb angle, which may indicate pathogenesis of AIS.

Keywords Adolescent idiopathic scoliosis · Magnetic resonance imaging · Spine · Spinal cord

Introduction

Magnetic resonance imaging (MRI) is widely applied in evaluating spine cord in idiopathic scoliosis. In review of literature, documented data of MRI study are rarely found in normal adolescents and few whole-spine column and cord measurements and their correlation with Cobb angle were studied [14]. The hypothesis being examined is that in some patients with scoliosis, there is disproportionate neuro-osseous growth. The longitudinal growth of the spinal cord fails to keep pace with the growth of the vertebral column and, as a consequence, the spine buckles into a scoliosis deformity [13, 15].

In this study, MRI and multiplane 3D reconstruction of the spine and hindbrain was performed in 49 AIS patients and 41 healthy adolescent volunteers using 1.5-T MR Scanner. We sought to determine the sagittal-sectional and cross-sectional morphologic changes of the spinal cord and spine in AIS and confirm the hypothesis that uncoupled

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neuro-osseous growth existed in AIS. The results were also correlated with Cobb angle.

Volunteers and methods

Subjects

The 41 healthy adolescents were randomly recruited from local schools, with average age 14 (11–17 years old). 18 of them were male, and 23 of them were female. All subjects were carefully assessed according to the requirements: careful physical examination to rule out any known abnormalities of the spine and spinal cord, no abnormal finding on whole-spine MRI scan, ethical approval from the ethics committee of PUMC hospital and informed consent from all subjects and their parents have been obtained.

The 49 AIS subjects were hospitalized in spinal center of PUMC hospital between September 2007 and July 2009 with average age 14 (12–16 years old). 19 of them were male, and 30 of them were female. The average Cobb angle was 45.6°. PUMC Classification [16] of AIS as follows: PUMCI19 cases (Ia: 14 cases, Ib:5 cases), PUMCII22 cases (IIa:4 cases, IIb1:6 cases, IIb2:3 cases, IIc1: 3 cases, IIc2:2 cases,IIc3:4 cases), PUMCIII 8 cases (IIa:5 cases, IIb:3 cases). All subjects were carefully assessed according to the requirements: definite diagnosis of AIS with exclusion of other types of scoliosis or kyphosis, major curve located between T7 and T12, complete material of MRI and X-ray, ethical approval and informed consent were obtained.

MRI assessment

MRI examination and multiplane 3D reconstruction of the spine and hindbrain was performed in all subjects using 1.5-T MR Scanner (Philips, Holland) with a spine array coil. Sagittal scans of the whole spine from foramen magnum to sacrum and transverse (TS) image of the vertebral column were obtained in the supine position. Scan parameters as follows: (i) sagittal, T1WI: TR/TE = 400/8 ms, Turbo factor = 5, NSA = 4, T2WI: TR/TE = 3,000/120 ms, Turbo factor = 52, NSA = 6; (ii) axial, T2WI: TR/TE3000/120 ms, Turbo factor = 24, NSA = 4; (iii) MRM: TR/TE = 8,000/1,000 ms, Turbofactor = 250, NSA = 2. All the measurements were performed on a workstation (Easy-Vision, Philips Medical Systems, Best, Holland), which allowed simultaneous display of the sagittal, coronal and axial views of the vertebral column. Cross-sectional measurement of the cord was made at the midpedicle level on a true axial plane, which was parallel to the superior endplate of that particular vertebra.

The maximum TS diameter and the largest AP diameter of the cord of were measured at the selected cross-sectional plane of the vertebra. Then we got AP/TS ratio. Lateral cord space (LCS) was defined as formula: $(A + C/2)/(B + C/2)$ to reflect the position of the cord (Fig. 1a). The distances *A*, *B* and *C* referred to the distance between the parallel lines along the surface of the cord and vertebral canal. The area of spinal cord and vertebral canal was also taken at the same level with shape-measuring tool available in the workstation program (Fig. 1b).

The length of cord and vertebral column was obtained using a distance-measuring tool available in the workstation program. At the mid sagittal section of spine, length of cord and vertebral column was measured from the tip of odontoid process (C2) down to the inferior endplate of L5 and the conus medullaris, respectively. In AIS group, MRI multiplane 3D images of the whole spine was reconstructed first and the matched 3D length of cord or vertebral column was measured (Fig. 2). The tip of conus medullaris was defined in relation to the upper, middle, or lower third of the adjacent vertebral body, as the same method described by Saifuddin et al. [20] (Fig. 1c). The level of the cerebellar tonsil related to the basion-opsithion (BO line) was measured according to the method described by Aboulezz et al. [1]. Distance taken above the BO line was conventionally assigned as positive value while distance taken

Fig. 1 **a** The distance of lateral cord space to the right side of the cord is defined as *A*; while the distance of lateral cord space to the left side of the cord is defined as *B*; *C* equals the cord diameter. A ratio is calculated with the formula $(A + C/2)/(B + C/2)$, which is known as the lateral cord space (LCS) ratio, to reflect the relative position of cord, **b** thoracic cord area, **c** location of conus medullaris, **d** cerebellar tonsillar level related to the basion-opsithion (BO) line, odontoid process level related to the BO line, angle between axis of medulla oblongata and cervical cord (α), angle between axis of medulla oblongata and BO line (β)

Fig. 2 A 15-year-old girl with severe thoracic scoliosis (Cobb Angle 46°). **a** Sagittal scan of AIS patient. **b** 3D reconstruction showing the thoracic curve. **c** 3D reconstruction showing vertebral canal and spine cord. **d** Measurement route of vertebral column after 3D reconstruction

below the BO line was defined as negative value. Similarly, distance of atlas odontoid process related to the BO line was measured. Besides, angle between axis of cervical vertebra and medulla oblongata (α), angle between axis of BO line and medulla oblongata (β) was obtained (Fig. 1d).

All the above measurements were obtained by two different investigators. The interclass correlation coefficients of different parameters range from 0.943 to 0.976, revealing a very high interobserver reliability. Measurement was checked for validity with precision of up to 0.1 mm.

Statistics

All the MRI parameters were expressed as mean value. Linear regression was performed to test the effect of age on various parameters. *t* test was used to compare the different MR parameters between AIS group and control group. Pearson correlation coefficient and Spearman correlation coefficient were used to explore the correlation between MRI parameters and Cobb angle. SPSS version 13.0 was used for all statistical analysis. Statistical significance was considered with $P < 0.05$.

Results

Spinal cord length, vertebral column length and their ratio

Spinal cord length and vertebral column length was not significantly different between AIS and control group, but spinal cord length/vertebral column length ratio is

Table 1 Comparison of MRI variate between AIS and control

MRI variate	AIS (<i>n</i> = 49)	Control (<i>n</i> = 41)	<i>t</i>	<i>P</i>
Standing height (mm)	160.20	159.78	0.388	0.702
Cervical length (mm)	117.61	111.90	1.66	0.100
Thoracic length (mm)	260.06	260.73	−0.16	0.877
Lumbar length (mm)	145.78	151.47	−1.23	0.225
Total cord length (mm)	391.01	399.34	−0.68	0.505
Total vertebral length (mm)	543.06	524.10	1.97	0.054
Cord/vertebral length ratio	0.72	0.75	−5.62	0.000

significantly smaller in AIS compared with control group ($P < 0.05$). Vertebral length, cord length and their ratio were not related with age or Cobb angle ($P > 0.05$). Cord/vertebral length ratio in mild, moderate and severe groups were significantly smaller than control group ($P < 0.01$) (Table 1). But there was no difference among mild, moderate and severe groups (one-way ANOVA test, $P > 0.05$).

AP, TS, AP/TS cord ratio, LCS, Cord area, Vertebral canal area and their ratio

The AP, TS, AP/TS cord ratio, LCS, cord area, vertebral canal area and cord area/vertebral canal area ratio were significantly larger in AIS group compared with control group ($P < 0.05$). The AP, AP/TS cord ratio, LCS, cord area and cord area/vertebral canal area ratio were significantly correlated with Cobb angle ($r = 0.187$ – 0.377 , $P < 0.05$) (Table 2).

Cerebellar tonsil level from BO line, odontoid process from BO line, α and β angle

Cerebellar tonsil level from BO line, odontoid process from BO line, α and β angle were significantly different between AIS and control group ($P < 0.05$). Cerebellar tonsillar level from BO line, odontoid process from BO line, α and β angle were not significantly correlated with Cobb angle (Spearman's coefficient correlation 0.034–0.099, $P > 0.05$). In AIS group, 38.3% of the patients had cerebellar tonsillar below BO line (median tonsillar position 0.85 mm above BO line, ranging from −4.14 to 6.30 mm) while only one volunteer (2.44%) in control group had cerebellar tonsillar below BO line (median tonsillar position 3.73 mm above BO line, ranging from −2.0 to 15.56 mm).

Position of conus medullaris

Conus medullaris was found to terminate at the level of L1 upper 1/3 on average (T_{11} upper 1/3– L_2 middle 1/3) in AIS group. Conus medullaris was found to terminate at the

Table 2 Correlation between MRI variate in AIS and Cobb angle

MRI variate	Mean	r_1	P	i_2	P
Standing height (mm)	160.20	−0.03	0.83	−0.08	0.517
AP (mm)	6.58	0.19	0.04	0.27	0.003
TS (mm)	7.28	−0.01	0.94	0.02	0.795
AP/TS	0.93	0.21	0.02	0.27	0.002
LCS	2.31	0.37	0.00	0.38	0.000
Position of medullary conus	4.42	−0.01	0.93	0.01	0.938
Cerebellar tonsillar to BO line (mm)	0.86	0.09	0.40	0.10	0.377
Odontoid process to BO line (mm)	6.46	−0.04	0.76	−0.04	0.721
Oblongata/cervical vertebrae (α)	21.94	0.08	0.47	0.04	0.750
Oblongata/BO line (β)	64.12	0.01	0.95	0.03	0.769
Cervical length (mm)	117.61	0.03	0.81	0.08	0.457
Thoracic length (mm)	260.06	−0.10	0.27	−0.09	0.312
Lumbar length (mm)	145.78	0.01	0.94	0.06	0.742
Total cord length (mm)	391.01	0.02	0.93	0.16	0.530
Total vertebral length (mm)	543.06	−0.12	0.63	−0.15	0.550
Cord/vertebral length ratio	0.72	0.18	0.47	−0.02	0.945
Cord area (mm ²)	38.78	−0.16	0.11	−0.15	0.131
Vertebral canal area (mm ²)	251.87	−0.11	0.24	−0.06	0.528
Cord/vertebral canal area ratio	0.20	0.07	0.44	0.21	0.022

r_1 Pearson correlation coefficient, r_2 Spearman's correlation

level of L1 lower 1/3 on average (T₁₂ lower 1/3–L_{2/3} disc level) in control group. The difference was significant compared with control group ($P < 0.01$). Position of conus medullaris was not related with Cobb angle ($r = 0.007$, $P > 0.05$).

Discussion

Scoliosis is a complex three-dimensional deformity and its pathogenesis is still unknown. Roth [17, 18] made the hypothesis of uncoupled neuro-osseous growth in AIS between 1968 and 1981, in which he explained idiopathic scoliosis as a disproportion of vertebro-neural growth due to either a short spinal cord or a too rapid growth spurt of the spine. Recently, Chu [4] reported a significantly reduced cord to vertebral length ratio was found in 14 AIS subjects when compared with controls, which was contributed mainly by the lengthening of thoracic segment of the vertebral column, whereas the absolute spinal cord length did not show equal proportion of lengthening in

AIS. MRI of the whole spine by 3D reconstruction makes it feasible to measure spinal cord length in AIS patients accurately [22], which would provide a critical test of Roth–Porter's hypothesis [2].

In this study, spinal cord length and vertebral column length are not significantly different between AIS and control group, but cord/vertebral length ratio is significantly smaller in AIS compared with control group ($P < 0.01$). LCS was significantly larger in AIS group compared with control group ($P < 0.05$) and was correlated with Cobb angle ($P < 0.05$). The cord was also found to deviate towards the concavity side. We propose that it is very likely that the spinal cord under a stretching tethering force along the longitudinal axis could lead to corresponding change in cross-sectional shape, from oval to a more rounded shape. The above theory was further supported by observation of consistency in shape change of cord at least two vertebral level above and below the apex, respectively. Disproportionate neuro-osseous growth might explain why the apex of scoliosis is frequently in the lower thoracic spine. The vertebral epiphyses close earlier in the upper region than in the lower thoracic spine [11], and the major component of adolescent longitudinal spinal growth takes place in the lower thoracic spine between T5 and T10 [18]. This part of the spine would be most vulnerable to deformity if at that time there was disproportionate growth.

For the hypothesis to be correct, one would expect evidence that the spinal cord can modify the growth of surrounding bone. Holtzer [8] thought that the spinal cord influences local bone growth during early development, much as the size of the brain determines the size of the skull. Recent research confirmed a close match between the vertebral canal and the size of the spinal cord in early life [10]. Accelerated bone growth would increase both leg length and vertebral growth, but the sitting height could be arrested whilst the curve progressed because of a short spinal cord.

In this study, the level of cerebellar tonsil was consistently found to be significantly more low-lying than healthy controls and was not correlated with Cobb angle or age (linear regression, $P > 0.05$). In our control group, 40 students (97.56%) had the cerebellar tonsillar level above the BO line (median tonsillar position 3.73 mm above BO line). Kim [9] had the similar finding. The low-lying tonsils had been reported [3, 7] and might be secondary to adjustment to the relatively shorter cord within the elongated vertebral column. Therefore, we speculate that the cord is likely to be under a stretching force along the longitudinal axis which is manifested by the change in cross-sectional shape. Furthermore, instead of locating in the center of the spinal canal, the cord deviates to the concavity side, which is reflected by a marked change in the ratio of LCS around the cord. This latter feature could

be due to both stretching force along the cord and adjustment of spinal cord to altered shape of the canal in the scoliotic spine.

Samuelsson et al. [21] performed whole-spine MRI in 26 patients with IS. In all four with tonsillar ectopia, the tonsils were less than 5 mm below the foramen magnum, but two were associated with syringomyelia. In the series reported by Royo-Salvador [19], among 231 patients with syringomyelia and scoliosis, 96.54% showed some descent of the cerebellar tonsils but less than 5 mm below the foramen magnum. The Chiari malformation and the syrinx could be the result of traction on the medulla distally through the foramen magnum. It is also possible that growth of the spinal cord is slower in patients with idiopathic scoliosis, resulting in a cord that is shorter than a more rapidly growing vertebral canal, or that reduced growth of the cord is the result of pineal dysfunction, perhaps involving a melatonin deficiency [12].

In this study, conus medullaris was found to terminate at the level of L1 upper 1/3 on average (T11 upper 1/3–L2 middle 1/3) in AIS group and at the level of L1 lower 1/3 on average (T12 lower 1/3–L2/3 disc level) in control group. The difference was significant compared with control group ($P < 0.01$). Saifuddin [20] reported that conus medullaris ranged from T12 middle 1/3 to L3 upper 1/3, mean level is L1 lower 1/3 in 690 healthy adults. Soleiman [23] found mean level of conus medullaris is L1 middle 1/3 (main age 20–80).

The relative shorter cord was the pathogenesis of AIS or the result of spinal deformity. Chu [4–6] reported that the cross-sectional shape of the cord in AIS was not due to compression from the wall of the spinal canal by observation that the cross-sectional shape of the cord in severe AIS was fairly symmetrical using the MetaMorph Imaging System. Because compression force from one side should result in asymmetrical shape of the cord. Similarly, on the sagittal plane, we need more experimental evidence for our hypothesis and successful establishment of AIS animal model by relative shorter cord would thoroughly support it.

Though the finding of morphologic change of the cord supports Roth–Porter pathogenetic hypothesis of disproportionate growth between the spinal cord and vertebral column, it does not go against other hypothesis of AIS pathogenesis, namely, uncoupled endochondral-membranous bone formation, asymmetry of skeletal growth, biomechanical mechanism, thoracospinal concept, neuro-developmental mechanism. We postulate that all the above mechanisms are probably different components of the same systemic abnormality involved in development of scoliosis.

In this study, we tried to explore the relationship of morphologic change of the cord and Cobb angle. The number of subjects was limited in each subgroup in the

statistical analysis. Next research program for larger number of subjects and routine 3D MRI analysis of AIS is planned.

Conclusion

Our study revealed the morphologic changes of cross-sectional configuration and relative shortened position of the cord. Some changes were significantly related with Cobb angle. This may provide some support to the hypothesis of uncoupled neuro-osseous growth along the longitudinal axis of spinal cord, which may indicate pathogenesis of AIS.

References

1. Aboulezz AO, Sartor K, Geyer CA, Gado MH (1985) Position of cerebellar tonsils in the normal population and in patients with Chiari malformation: a quantitative approach with MR imaging. *J Comput Assist Tomogr* 9:1033–1036
2. Burwell RG (2001) Comment to “The pathogenesis of idiopathic scoliosis: uncoupled neuro-osseous growth?” *Eur Spine J* 10:482–487
3. Cheng JCY, Chau WW, Guo X, Chan YL (2003) Redefining the magnetic resonance imaging reference level for the cerebellar tonsil: a study of 170 adolescents with normal versus idiopathic scoliosis. *Spine* 28:815–818
4. Chu WC, Lam WW, Chan YL, Ng BK, Lam TP, Lee KM, Guo X, Cheng JC (2006) Relative shortening and functional tethering of spinal cord in adolescent idiopathic scoliosis?: study with multiplanar reformat magnetic resonance imaging and somatosensory evoked potential. *Spine* 31:E19–E25
5. Chu WC, Man GC, Lam WW, Yeung BH, Chau WW, Ng BK, Lam TP, Lee KM, Cheng JC (2007) A detailed morphologic and functional magnetic resonance imaging study of the craniocervical junction in adolescent idiopathic scoliosis. *Spine* 32:1667–1674
6. Chu WC, Man GC, Lam WW, Yeung BH, Chau WW, Ng BK, Lam TP, Lee KM, Cheng JC (2008) Morphological and functional electrophysiological evidence of relative spinal cord tethering in adolescent idiopathic scoliosis. *Spine* 33:673–680
7. Gupta P, Lenke LG, Bridwell KH (1998) Incidence of neural axis abnormalities in infantile and juvenile patients with spinal deformity. Is a magnetic resonance image screening necessary? *Spine* 23:206–210
8. Holtzer H (1952) Experimental analysis of development of spinal column. Part 1. Response of pre-cartilage cells to size variations of spinal cord. *J Exp Zool* 121:121–148
9. Kim JT, Bahk TH, Sung J (2003) Influence of age and sex on the position of the conus medullaris and Tuffier line in adults. *Anesthesiology* 99:1359–1363
10. Knutsson F (1961) Growth and differentiation of the postnatal vertebra. *Acta Radiol* 55:401–407
11. Lord MJ, Ogden JA, Ganey TM (1995) Postnatal development of the thoracic spine. *Spine* 20:1692–1698
12. Maguire J, Madigan R, Wallace S, Leppanen R, Draper V (1993) Intraoperative long-latency reflex activity in idiopathic scoliosis demonstrates abnormal central processing. A possible cause for idiopathic scoliosis. *Spine* 18:1621–1626

13. Porter RW (2001) Can a short spinal cord cause idiopathic scoliosis? *Eur Spine J* 10:2–9
14. Porter RW (2001) The pathogenesis of idiopathic scoliosis: uncoupled neuro-osseous growth? *Eur Spine J* 10:473–481
15. Porter RW (2000) Idiopathic scoliosis: the relation between the vertebral canal and the vertebral bodies. *Spine* 25:1360–1366
16. Qiu GX, Zhang JG, Wang YP, Xu HG, Zhang J, Wen XS, Lin J, Zhao Y, Shen JX, Yang XY, Luk KD, Lu DS, Lu WW (2005) A new operative classification of idiopathic scoliosis: a Peking Union Medical College method. *Spine* 30:1419–1426
17. Roth M (1968) Idiopathic scoliosis caused by a short spinal cord. *Acta Radiol Diagn* 7:257–271
18. Roth M (1981) Idiopathic scoliosis from the point of view of the neuroradiologist. *Neuroradiology* 21:133–138
19. Royo-Salvador MB (1996) Syringomyelia, scoliosis and idiopathic Arnold–Chiari malformations: a common etiology. *Rev Neurol* 24:937–959
20. Saifuddin A, Burnett SJ, White J (1998) The variation of position of the conus medullaris in an adult population. A magnetic resonance imaging study. *Spine* 23:1452–1456
21. Samuelsson L, Lindell D, Kogler H (1991) Spinal cord and brain stem anomalies in scoliosis. MR screening of 26 cases. *Acta Orthop Scand* 62:403–406
22. Schmitz A, Jaeger UE, Koenig R, Kandyba J, Wagner UA, Giesecke J, Schmitt O (2001) A new MRI technique for imaging scoliosis in the sagittal plane. *Eur Spine J* 10:114–117
23. Soleiman J, Demaerel P, Rocher S, Maes F, Marchal G (2005) Magnetic resonance imaging study of the level of termination of the conus medullaris and the thecal sac: influence of age and gender. *Spine* 30:1875–1880